Please cancel claims 23 and 33 without prejudice or disclaimer.

Attached hereto is Appendix A which is the marked-up version of claims 14, 24, 25 and 34.

REMARKS

Claims 14, 24, 25, and 34 have been amended to define the invention with more clarity and particularity. Claims 23 and 33 have cancelled without prejudice or disclaimer. No new matter has been added to the specification as a result of the amendments. Claims 14-22, 24-32 and 34 remain before the Examiner. Applicants respectfully request reexamination and reconsideration of those claims in their presently amended form.

Objections

At pages 2 and 3 of the Action, the Examiner has set forth objections relating to priority claims, Information Disclosure Statements and trademarks. Applicants respectfully request that correction of these objections be held in abeyance until claims are allowed.

Rejections under the First Paragraph of 35 U.S.C. § 112

The Examiner has rejected claims 22 and 32 under the first paragraph of 35 U.S.C. § 112 for an alleged lack of enablement. In particular, the Examiner asserts that hybridoma ATCC 75408 is required to practice the claimed invention and that an affidavit or declaration is needed to assure removal of access restrictions following issuance of a patent. Enclosed herewith is the deposit receipt indicating that the deposit shall be available once a patent issues. In light of that receipt, this rejection is now moot.

Rejections under the Second Paragraph of 35 U.S.C. § 112

The Examiner has rejected claims 14-22 and 25-32 under the second paragraph of 35 U.S.C. § 112 as omitting needed steps and claims 14-34 as allegedly being indefinite for failing to precisely define "framework". Applicants respectfully argue against this rejection for the following reasons.

Applicants point out that the method of claims 14 and 25 need only comprise the recited steps. Other steps can be included. To expedite prosecution, however, claims 14 and 25 have been amended to include the additional steps of original claims 23 and 33, respectively. In light of these amendments, this rejection is now moot.

The phrase "framework region" as used in the context of immunoglobulin molecules (e.g., antibodies) is well known in the art. Enclosed herewith as Exhibit A are excerpts from a textbook entitled, "Fundamental Immunology", edited by William E. Paul, M.D., copyrighted in 1984. It can be seen from those excerpts that the phrase "framework region" is a well defined term known to those of skill in the art. In view of this art recognized definition, Applicants respectfully submit the use of the phrase "framework region" in the claims of the instant application is not indefinite and that one of ordinary skill in the art would readily appreciate the meaning of that phrase.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 14, 17-19, 25 and 28-30 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Caiman and Rajewsky (hereinafter "Cumano") in light of Higuchi. The Examiner asserts that Cumano teaches a method of producing an antibody combining site using oligonucleotides that have 3' and

5' termini, framework regions and an $[NNK]_n$ sequence as recited by the claims. Applicants argue against this rejection for reasons set forth below.

The rejected claims provide a method for producing an antibody combining site using induced mutagenesis of a CDR region using an oligonucleotide primer having a 5' portion that hybridizes to a framework region of an immunoglobulin light chain, a mutagenic portion defined by the formula $[NNK]_n$, and a 3' portion that hybridizes to a framework region of the same immunoglobulin light chain gene. The Cumano cited art does not teach, suggest or even mention the use of oligonucleotide primers for mutagenizing CDR portions of immunoglobulin light chain gene. Contrary to the assertions of the Examiner, the sequences set forth in Figures 1 and 2 of Cumano are not oligonucleotide primers. Rather they represent nucleotide sequences of portions of antibodies isolated from particular hybridomas. To make a sequence of Figures 1 and 2 of Cumano read on the presently claimed invention, it is necessary to remove triplet codons from the sequences of both Figure 1 and Figure 2. By way of example, to make the Vγ1 sequence of Figure 1 read on claim 1, the Examiner found it necessary to remove the codon "TCA" at the beginning of the CDR 1 region as well as condons "ACA *et seq.*" from that same CDR 1 region. Similarly in Figure 2, the Examiner has found it necessary to remove from the V186.2 sequence, triplet codons beginning with TAC *et seq.*

The cited Cumano art does not teach mutagenesis whatsoever let alone the use of a particular triplet codon for accomplishing such mutagenesis. Cumano is nothing more than disclosure of nucleotide sequences of portions of antibodies obtained from hybridomas and/or immunized animals. Cumano cannot be viewed as teaching any process for mutagenizing an immunoglobulin light chain gene, nor the use of any oligonucleotide primers for

accomplishing such mutagenesis.

The deficiencies of Cumano cannot be cured by Higuchi, which is cited by the Examiner as disclosing only that PCR can be used to introduce alterations into DNA. That is, a combination of Cumano and Higuchi does not lead an artisan to the presently claimed invention.

In view of the above, Applicants respectfully request the rejection of the claims on the basis of Cumano be withdrawn.

SUMMARY

In light of the amendments to the claims and for the reasons set forth above, Applicants respectfully submit that the claims are now in a condition of allowance. An early notification to that effect is hereby earnestly solicited.

Respectfully submitted,

4-02-2002
DATE

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APPENDIX A

Marked-Up Version of Amended Claims

14. (Amended) A method for producing an antibody combining site in a polypeptide comprising inducing mutagenesis in a complementarity determining region (CDR) of an immunoglobulin light chain gene which comprises amplifying a CDR portion of the immunoglobulin gene by polymerase chain reaction (PCR) using a PCR primer oligonucleotide, said oligonucleotide having 3' and 5' termini and comprising:

a) a nucleotide sequence at said 3' terminus capable of hybridizing to a first framework region of an immunoglobulin gene;

b) a nucleotide sequence at said 5' terminus capable of hybridizing to a second framework region of an immunoglobulin gene; [and]

c) a nucleotide sequence between said 3' and 5' termini according to the formula:

$$[NNK]_n,$$

wherein N is independently any nucleotide, K is G or T, and n is 3 to about 24, said 3' and 5' terminal nucleotide sequences having a length of about 6 to 50 nucleotides, or an oligonucleotide having a sequence complementary thereto[.] ;

d) isolating the amplified CDR to form a library of mutagenized immunoglobulin light chain genes;

e) expressing the isolated library of mutagenized light chain genes in combination with one or more heavy chain genes to form a combinatorial antibody library of expressed heavy and light chain genes; and

f) selecting species of said combinatorial antibody

library for the ability to bind a preselected antigen.

24. (Amended) The method of claim [23] 14 wherein said one or more immunoglobulin heavy chain genes is a library of heavy chain genes.

25. (Amended) A method for producing an antibody combining site in a polypeptide comprising inducing mutagenesis in a complementarity determining region (CDR) of an immunoglobulin light chain gene which comprises amplifying a CDR portion of the immunoglobulin gene by polymerase chain reaction (PCR) using a PCR primer oligonucleotide, said oligonucleotide having 3' and 5' termini and comprising:

a) a nucleotide sequence at said 3' terminus capable of hybridizing to a first framework region of an immunoglobulin gene;

b) a nucleotide sequence at said 5' terminus capable of hybridizing to a second framework region of an immunoglobulin gene; and

c) a nucleotide sequence between said 3' and 5' termini according to the formula:

$$[MNN]_n,$$

wherein N is independently any nucleotide, M is A or C, n is 3 to about 24, said 3' and 5' terminal nucleotide sequences having a length of about 6 to 50 nucleotides, or an oligonucleotide having a sequence complementary thereto[.] ;

d) isolating the amplified CDR to form a library of mutagenized immunoglobulin light chain genes;

e) expressing the isolated library of mutagenized light chain genes in combination with one or more heavy chain

genes to form a combinatorial antibody library of expressed heavy and light chain genes; and

f) selecting species of said combinatorial antibody library for the ability to bind a preselected antigen.

34. (Amended) The method of claim [33] 25 wherein said one or more immunoglobulin heavy chain genes is a library of heavy chain genes.